

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

15 Dec 2005

X16566

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/038232

International filing date (day/month/year)
08.12.2004

Priority date (day/month/year)
15.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07C235/20, A61K31/192, A61P3/10

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1 (a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Seufert, G

Telephone No. +49 89 2399-8330



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/038232

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/038232

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 8-21 with regard to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 8-21 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/038232

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-23
	No: Claims	
Inventive step (IS)	Yes: Claims	1-23
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-7, 22, 23
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following document:

D1 WO-A-03051821

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 8-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability

Novelty

The present application refers to phenyl propionic acid derivatives of the general formula (I) (claim 1) and pharmaceutical compositions comprising them (claim 6). The compounds are peroxisome proliferator activated receptor (PPAR) modulators, especially PPARY modulators and thus are useful in the treatment of conditions modulated by PPAR (claims 8- 23).

None of the prior art documents discloses a compound falling within the scope of formula (I). Claim 1 as well as the claims 2-23, therefore, appear to meet the requirement of Art. 33(2) PCT.

Inventive step

Document D1, which may be considered as the most relevant state of the art, describes a structurally very similar compound, which acts as an agonist of PPAR α and PPARY (see D1, page 3, lines 25-27 and example 2). The presently claimed

compounds are distinguished from the one disclosed in D1 in that the nitrogen of the amide group is unsubstituted and the phenyl group attached via an ethylene group to the amide nitrogen is substituted by a group OR².

The problem to be solved by the present invention may therefore be regarded as providing further compounds useful as PPAR modulators.

The problem has been solved by the presently claimed compounds (see application, biological assays, pages 22-27).

Neither D1 nor any other available document gives an indication to the skilled person, which would motivate him to modify the prior art compound in such a way as to arrive at the presently claimed compounds in order to solve the aforementioned problem. It was also not foreseeable that the modifications of the compound of D1, which would be necessary to arrive at the presently claimed compounds, would result in a compound having the desired PPAR activity. In addition, the presently claimed compounds are high affinity PPAR γ partial agonists, while the compound of D1 seems to be more potent with respect to PPAR α (see D1, page 27, lines 21-25). The subject-matter of claims 1-23 may therefore be considered as involving an inventive step (Art. 33(3) PCT).

Industrial applicability

For the assessment of the present claims 8-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

There are no objections against the industrial applicability of the subject-matter of claims 1-7, 22 and 23.

Further remarks:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

Claim 7 comprises all the features of claim 6 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT). The same applies to claim 23, which should have been dependent on claim 22. Diabetes is a condition modulated by a PPAR (claim 22).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X-16566	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/US2004/038232	International filing date (<i>day/month/year</i>) 08/12/2004	(Earliest) Priority Date (<i>day/month/year</i>) 15/12/2003
Applicant ELI LILLY AND COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/038232

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C235/20 A61K31/192 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 03/051821 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; ALSTERMARK LINDSTEDT, EVA-LOTT) 26 June 2003 (2003-06-26) page 3, line 25 - line 27; claims; example 2</p>	1-23
A	<p>US 6 294 580 B1 (WILLSON TIMOTHY MARK ET AL) 25 September 2001 (2001-09-25) column 2, line 16 - line 31 column 91, line 50 - column 94, line 53; claims; examples</p>	1-23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 April 2005

Date of mailing of the international search report

14/04/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seufert, G

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/038232

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/038232

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03051821	A	26-06-2003	AU 2002352427 A1	30-06-2003
			AU 2002366315 A1	30-06-2003
			BR 0214986 A	14-12-2004
			BR 0214988 A	14-12-2004
			CA 2469302 A1	26-06-2003
			CA 2470491 A1	26-06-2003
			EP 1458672 A1	22-09-2004
			EP 1458673 A1	22-09-2004
			WO 03051821 A1	26-06-2003
			WO 03051822 A1	26-06-2003
			HU 0402022 A2	28-01-2005
			HU 0402133 A2	28-02-2005
<hr/>				
US 6294580	B1	25-09-2001	AT 205485 T	15-09-2001
			AU 717699 B2	30-03-2000
			AU 2093597 A	16-09-1997
			BG 102792 A	31-08-1999
			BR 9707786 A	27-07-1999
			DE 69706658 D1	18-10-2001
			DE 69706658 T2	20-06-2002
			DK 888317 T3	21-01-2002
			EA 1403 B1	26-02-2001
			EE 9800288 A	15-02-1999
			EP 0888317 A1	07-01-1999
			HK 1015369 A1	15-02-2002
			HU 0004845 A2	28-05-2001
			IL 125796 A	14-06-2001
			JP 3255930 B2	12-02-2002
			JP 2000507216 T	13-06-2000
			NO 983940 A	27-10-1998
			NZ 331381 A	23-06-2000
			PL 328871 A1	01-03-1999
			SI 888317 T1	30-04-2002
			SK 116398 A3	13-04-1999
			AP 780 A	22-11-1999
			CA 2247443 A1	04-09-1997
			CN 1218460 A ,C	02-06-1999
			CY 2319 A	14-11-2003
			CZ 9802750 A3	13-01-1999
			WO 9731907 A1	04-09-1997
			ES 2163125 T3	16-01-2002
			HR 970110 A1	30-04-1998
			ID 15985 A	21-08-1997
			OA 10843 A	14-08-2001
			PT 888317 T	28-03-2002
			TR 9801707 T2	21-12-1998
			ZA 9701645 A	10-12-1997
<hr/>				

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/037189

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0191754	A1	06-12-2001	AU	6419201 A		11-12-2001
			CA	2409597 A1		06-12-2001
			EP	1284734 A1		26-02-2003
			JP	2003534379 T		18-11-2003
			US	2004019077 A1		29-01-2004

WO 2005011697	A	10-02-2005	WO	2005011697 A2		10-02-2005

WO 2004094386	A	04-11-2004	WO	2004094386 A1		04-11-2004
